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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,211	04/13/2004	Rainer Haag	20945 US1	4641

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,211	HAAG ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,16 and 23-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,17-22 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group III, claims 1-30, wherein X^1 and X^2 are CH in Paper filed on 11/8/2004 is acknowledged. Claims 1-4, 7-14, 17-22 and 27-30 will be examined to the extent they embrace the elected subject matter.

The traversal is mainly on the ground(s) that claims there is no serious search burden to examine all three groups and that they share the same utility This is not found persuasive. The following apply.

1. First of all, as noted in the previous office action, Invention I, II, and III are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core namely pyrimidine versus pyridine versus benzene core along with various heterocyclic cores embraced in the instant R group.

   Furthermore, it is mandatory classify and search these entire heterocyclic cores which are controlling and with limited time available per case, it would be a serious search burden to search all these heterocyclic cores.

   As can be seen form the number of prior art applied, there is a large number of compounds known in the literature which are also embrace in the instant claims The prior art which reads on the instant elected subject matter need not anticipate the non-elected subject an

2. Applicants have not provided any evidence that all these cores are equivalent.

   See the following paragraph provided in the previous office action:

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

3. Contrary to applicants' urging based on the references provided in the Information Disclosure Statement and the art applied , all core do not share the same utility.

The requirement is still deemed proper and is therefore made **FINAL.**

Claims 5-6, 15-16 and 23-26, which was inadvertently included in Group III, are withdrawn from consideration as they embrace non-elected subject matter.

In summary claims 1-4, 7-14, 17-22 and 27-30 are under examination.

Information Disclosure Statement

References cited in the Information Disclosure Statement filed on 4/13/2004 are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, 19-22 and 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any

claim not specifically rejected is rejected as being dependent on a rejected claim and have the same scope.

1. In claim 1, recitation of the term "prodrug" is deemed as indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable R and Y, groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

   Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means

can be clearly expressed in terms that are more precise. Applicants offer no structural guidance as to which derivatives are intended.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human

at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in the passage spanning line 32, page 12 to line 11, page 13. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. I) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of colon cancer or leukemia, does not reasonably provide enablement for producing anti-cancer effect on all or any cancer as recited in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "treating cancer" and "treating tumor cell proliferation". The scope of the claims includes any or all cancer even those wherein mode of action is not defined and those wherein histone acetylation inducers are

involved for which there is no enabling disclosure. In addition, the scope of the claim 27 and 30 includes treatment of any or all cancer or tumor cell proliferation, both of which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 21-22. The instant compounds are disclosed to have histone acetylation inducing activity and it is recited that the instant compounds are therefore useful in treating any or all cancer or tumor cell proliferation, for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as histone acetylation inducing activity that would be useful for all sorts of cancers and tumor cell proliferation. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be

effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Mahlknecht et al. Mol. Med. 6(8): 623-44, 2000 (PubMed Abstract), which suggests that current status at best exploratory and need further experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating cancer or tumor cell proliferation that require histone acetylation inducing activity or any other mode of action.

2) The state of the prior art: A very recent publication expressed that the histone acetylation inducing activity effects are unpredictable and are still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of histone acetylation inducers are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all cancers including those yet to be related to histone acetylation inducing activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general,

and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hatchard et al. J. Org. Chem., 29: 665-668,1964.

Hatchard discloses 3,5-bismethylsulfanyl-iosthiazole-4-carboxylic acid –2-amino-anilide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Zarin et al. Chem.Heterocycli. Compd (Engl. Transl.) 10: 96-98,1974.

Zarin et al teaches piperidine-3-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Gortinskaja et al. Zh. Obshch. Khim. 25: 2313-2115, 1955.

Gortinskaja et al teaches piperazine-2-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Balaban et al. J. Chem. Soc. 127: 2710, 1925.

Balaban et al teaches imidazole-4-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Holan et al. J. Chem. Soc. 1967: 20-25, 1967.

Holan et al teaches IH-Benzoimidazole-2-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Prewysz-Kwinto et al. Chem.Heterocycli. Compd (Engl. Transl.) 23: 624-627,1987.

Prewysz-Kwinto et al. teaches 7-ethyl-3-methyl-benzofuran-2-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hudkins et al. Heterocycles, 41(5): 1045-1050, 1995..

Hudkins et al. teaches 1H-indole-2-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Zalesov et al. Russ. J. Org. 31(8): 1104-1108, 1995.

Zalesov et al. teaches quinoxaline-2-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Salakhov et al. Russ. J. Org. 35(3): 397-401, 1999.

Salakhov et al. teaches 3-cyclohexene-6-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims.

Claims 4, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Friedrich et al. US 3,810,910.

Friedrich et al. teaches thiophene-4-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims. See example 4 on column 8.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Vyas et al. J. Indian Chem. Soc. 68: 294-295, 1991.

Vyas et al. teaches 8-methoxycoumarin-3-carboxylic acid (2-amino-phenyl) amide which is also generically claimed in the instant claims. See page 295.

Claims 4 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Rastogi et al. Indian J. Chem. Soc. 21B: 485-487, 1991.

Rastogi et al. teaches benzofuran-2-carboxylic acid (2-amino-phenyl) amide which is also claimed in the instant claims. See compound 5 on page 485 and also see compound 2 on page 485.

Claims 1, 2, 4, 19 and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. EP 0 847 992

Suzuki et al. teaches monoacylated-O-phenyldiamines, which are also generically claimed in the instant claims, for treating hematologic malignancy. See entire document. Especially see compound of formula I and formula III on pages 3-4. See Table 3 for various heterocyclic acid amide of orthophenyldiamine0n pages 36-38.

Search is limited to R as aromatic heterocyclic group based on the elected species.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-14, 17-22 and 27-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-11, 17-18 and 34-47 of copending Application No. 10/212,901. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims overlaps with the stated

claims of 10/212,901. Note the compounds, composition and method of use taught by the copending application overlap with those claimed in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Venkataraman Balasubramanian

Venkataraman Balasubramanian

1/24/2005